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99 JUL 19 A9:15

JUL 16 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-0674
Draft Guidance for Industry on INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format

Dear Sir/Madam:

Reference is made to the above-noted Draft Guidance originally published in the Federal Register on 21 April 1999, Docket Number 99D-0674.

At this time, on behalf of The R.W. Johnson Pharmaceutical Research Institute (RWJPRI), we wish to provide our comments to this Draft Guidance. Our comments are both General and specific and are identified as such.

We greatly appreciate the opportunity to comment on this document and look forward to similar opportunities in the future.

Very truly yours,

for D. B. Panasewicz
for Donna Panasewicz
Director
Regulatory Affairs

Attachment

99D-0674

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The following comments and suggestions are being respectfully submitted in response to the issuance of the Draft Guidance for Industry on INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format.

General Comments:

The items listed below in the Specific Comment area basically address the fact that even during Phase 3, development of the drug product is ongoing. Based on this, some of the requirements are too restrictive, not allowing development to proceed without significant changes to the CM&C section.

Specific Comments: (preceded by line number)

148: We would add: "*If applicable*" to the beginning of the sentence: "*An updated detailed flow diagram for the synthesis or manufacturing process should be provided.*"

189: "*Any changes in the specification should be reported.*" The Agency does not identify how these changes should be reported, i.e., as an update to the annual report, as an amendment? Amendments take significant time and slow down the development process.

219: We would add: "*A summary of*" to the beginning of the sentence: "*Preliminary stability data based on representative material should be provided.*"

234: "*A batch formula should be provided, if not already submitted.*" Batch scale changes may still be made with each batch during these phases of investigation. We would, therefore, revise this sentence to read: "*A representative batch formula should be provided, if not already submitted*".

239–249: The paragraph talks about non-compendial excipients. It reads: "*Information for excipients not included in previously approved drug products should be equivalent to that submitted for new drug substances*". In the sentence prior to this it states that the manufacture and control of these substances can be referenced in a DMF, etc.

Our comment is that we do not normally provide data similar to drug substances for excipients. We do extensive impurity profiling of drug substances to learn what impurities are always present and their levels so we can set specifications. We also do degradation studies on drug substances to identify the degradation pathway and to set specifications. We do not agree that the same level of extensive testing should be required for excipients.

The way the paragraph reads it implies that we would have to provide this type of information in our INDs and NDAs. This should not be required.

241: "*Changes in acceptance testing for active ingredients...should be provided.*" The Agency does not identify how these changes would be provided , i.e., as an update to the annual report, as an amendment? Amendments take significant time and slow down the development process.

276: "*Changes to the specification should be reported.*" The Agency does not identify how these changes would be reported, i.e., as an update to the annual report, as an amendment? Amendments take significant time and slow down the development process.

340: "*A list of all firms associated with the manufacturing and controls... including contract labs...*". Additional contract sites for testing or even manufacturing and packaging could be added during these phases of an investigation. Could these sites be covered by indicating in the IND that other cGMP compliant company approved sites may be added?

425: Stress studies are usually not done until near the end of development; this information would not necessarily be ready for the Phase 3 IND.

460: "*Quantitative information should be reported for the batch formula.*" As an example, other batch sizes may still be produced through Phase 3 development.

464-475: For compendial excipients the Agency is asking for functional tests when necessary. These are tests beyond the compendia. Functional tests should always be optional. For non-compendial excipients, same comment as in lines 239-249.

522: "*...the name of the manufacturer and supplier* [for packaging materials] *should be provided.*" This is restrictive; we may be using more than one package type and a final market image package may not have been selected. A general description of the packaging should be adequate here.

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